American Journal of Medical Genetics 64:465–472 (1996)

Holoprosencephaly: Epidemiologic and Clinical Characteristics of a California Population

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Holoprosencephaly is a brain defect resulting from incomplete cleavage of the embryonic forebrain. It involves forebrain and facial malformations that can range from mild to severe. The epidemiology of holoprosencephaly is largely unknown. Published prevalence estimates have been derived from clinic-based case series, and suggested risk factors for holoprosencephaly have been identified in case reports, without confirmation from systematically conducted population-based studies. Using data from a population-based birth defects registry in California, we describe the epidemiologic and clinical characteristics of cytogenetically and phenotypically distinct types of holoprosencephaly. A total of 121 cases was identified among a cohort of 1,035,386 live births and fetal deaths. The prevalence of holoprosencephaly was 1.2 per 10,000 births (95% confidence interval 1.0–1.4 per 10,000). Of all cases, 41% (50/121) had a chromosomal abnormality, most commonly Trisomy 13. Among the 71 cytogenetically apparently normal cases, 18 had recognizable syndromes and the remaining 53 were of unknown cause. Among the cytogenetically abnormal cases, females had a greater risk than males (odds ratio = 2.3, 95% confidence interval [1.2, 4.4]). Among the cytogenetically normal cases, increased risks were observed among Hispanic whites (OR = 1.8 [0.9, 3.6]) and cases whose mother was born in Mexico (OR = 2.2 [1.0, 4.5]). Approximately 46% of all cases had alobar holoprosencephaly, the most severe form of the forebrain malformation. The facial phenotype did not strongly predict the severity of the brain defect; however, severity was inversely correlated with length of survival. This study is the first to present findings based on such a large population-based series of infants/fetuses affected by holoprosencephaly, and demonstrates the importance of investigating the component subgroups of this rare phenotype.

KEY WORDS: holoprosencephaly, epidemiology, alobar

INTRODUCTION

Holoprosencephaly, a rare brain defect resulting from incomplete cleavage of the embryonic forebrain, is thought to arise following interference with the induction of prechordal mesoderm during gastrulation [Webster, 1988; Siebert et al., 1990; Yakovlev, 1959]. It can be viewed as a malformation complex or developmental field defect involving the forebrain and face. Forebrain malformations range from mild (arrhinencephaly and some cases of agenesis of the corpus callosum) to alobar (complete) holoprosencephaly. Mild forms of facial changes are flat nasal bridge, hypotelorism, and single central incisor; more severe forms include median cleft lip, cebocephaly, ethmocephaly, and cyclopia [DeMyer et al., 1964].

Although largely unknown, the cause of holoprosencephaly is clearly heterogeneous. Holoprosencephaly has been observed frequently in chromosomal abnormalities and monogenic syndromes [Cohen, 1989a; Muenke, 1989]. Suggested non-genetic risk factors include maternal diabetes [Barr et al., 1983], retinoic acid [Lammer et al., 1985], salicylates [Benawra et al., 1980; Khudr and Olding, 1973; Agapitos et al., 1986], alcohol [Ronen and Andrews, 1991; Bönnemann and Meinecke, 1991; Jellinger et al., 1981], estrogen/progestin [Stabile et al., 1985], anticonvulsants [Holmes and Harvey, 1994], low-calorie weight reducing diets [Ronen, 1992], prenatal infections with cytomegalovirus [Byrne et al., 1987], rubella [Probst, 1979], toxoplasma [Lison et al., 1967], poverty [Roach et al., 1975], and previous pregnancy loss [Matsunaga and Shiota, 1977]. Most of these suggested risk factors were identified anecdotally in case reports or small,

Received for publication July 24, 1995; revision received January 12, 1996.

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unselected case series, without confirmation by systematically conducted studies.

We describe here the prevalence and clinical characteristics of holoprosencephaly and examine potential risks associated with several routinely collected infant and parental characteristics for cytogenetically and anatomically distinct types of holoprosencephaly using data from a population-based birth defects registry of over one million live births and fetal deaths in California.

MATERIALS AND METHODS

Cases were identified by the California Birth Defects Monitoring Program (CBDMP), which maintains a population-based congenital malformation registry with ascertainment from multiple sources [Croen et al., 1991]. Diagnostic and demographic information on malformed fetuses and live born infants is collected by CBDMP staff from medical records at hospitals and medical genetics centers. Nearly all structural anomalies diagnosed within one year after birth, including those prenatally diagnosed, are ascertained. However, ascertainment of malformations among fetuses from electively or spontaneously terminated pregnancies is conditional on diagnoses being made in hospitals or genetic centers, and thus is incomplete.

Considered for potential inclusion as cases were live births and fetal deaths (≥20 weeks of gestation) with a diagnosis of holoprosencephaly, possible holoprosencephaly, arrhinencephaly, proboscis or single nostril, cyclopia, aprosencephaly, or holotelencephaly from among the cohort of 1,035,386 live births and fetal deaths delivered between January 1983 and December 1988 to residents of selected California counties. For each infant or fetus with any of these diagnoses, eligibility was determined by a medical geneticist (E.J.L.), who reviewed prenatal ultrasonographic, brain imaging, and autopsy reports. Only infants or fetuses with incomplete cleavage of the cerebral forebrain were considered to have holoprosencephaly. Infants or fetuses with the following diagnoses were excluded if the diagnosis was not associated with holoprosencephaly: partial or complete absence of the corpus callosum, median cleft lip, short prolabium, arrhinencephaly, hydrocephalus, and encephalocele. Cases were also excluded if the forebrain malformation resulted from amniotic band disruption, porencephaly, or schizencephaly. A total of 121 holoprosencephaly cases was identified and formed the analytic base for this study.

Cases were classified into two main groups according to cytogenetic findings: cytogenetically abnormal and cytogenetically normal. For selected analyses, cytogenetically normal cases were subclassified into syndromal and nonsyndromal holoprosencephaly. Infants with syndromal holoprosencephaly were those with diagnoses consistent with a known monogenic disorder or recognizable pattern of malformation, infants of diabetic mothers, or infants with a family history consistent with one of the dominant or recessive holoprosencephaly syndromes (first degree relative with a diagnosis consistent with the holoprosencephaly spectrum: holoprosencephaly, arrhinencephaly, microcephaly, cleft lip, or single central incisor). Information on family history was not systematically collected, and was limited to what was present in the proband's medical records.

The severity of the forebrain defect was used to anatomically classify each case into alobar (small single ventricular cerebrum; no interhemispheric division), semilobar (rudimentary cerebral lobes; incomplete interhemispheric fissure), or lobar (well formed cerebral lobes; distinct interhemispheric fissure) holoprosencephaly following the classification scheme of DeMyer et al., [1964]. To examine the relationship between the severity of the brain and facial defects, chromosomally normal cases were subtyped on the basis of facial changes according to a modification of the DeMyer classification scheme [Siebert et al., 1990]. Categories included cyclopia (single median eye with or without proboscis), ethmocephaly (hypotelorism with proboscis between the eyes), cebocephaly (hypotelorism with single-nostril nose inferior to the eyes), median cleft lip, agnathia, and less severe facies (including hypotelorism).

A control group of 5,000 non-malformed infants was randomly selected from all infants born alive between 1983 and 1988 whose mothers resided in the same counties from which the cases derived. This control group was used to investigate possible relationships between holoprosencephaly and the child's sex (male vs. female), maternal and paternal race/ethnicity (white, non-Hispanic; white, Hispanic; black, non-Hispanic; Asian, non-Hispanic; other, non-Hispanic; other, Hispanic), maternal birthplace (California, other U.S. state, Mexico, other country), maternal and paternal age (<20, 20–24, 25–29, 30–34, >34), plurality (singleton vs. twins or more), and parity (0, 1, 2, or 3+ previous livebirths). Information on these characteristics came from the electronic birth certificate data files for both cases and controls. The odds ratio (OR) and its 95% confidence interval (CI) were used to estimate potential risks for holoprosencephaly associated with several parental and infant characteristics [EGRET, 1991].

RESULTS

A total of 121 holoprosencephaly cases was identified, yielding an overall prevalence of 1.2 per 10,000 live births and fetal deaths (95% confidence interval = 1.0–1.4). Results of cytogenetic testing were available for 92 of the cases (76%), of which 43 were found to have abnormal results. In addition to these 43 cases, 7 additional cases were classified as cytogenetically abnormal because they were clinically consistent with Trisomy 13 even though cytogenetic results were not available. Based on these 50 cases (41% of the total), the prevalence of cytogenetically abnormal holoprosencephaly was 0.48 per 10,000 live births and fetal deaths. Of the remaining 71 cases, 18 (approximately 25%) had a recognizable syndrome and 53 (75%) were considered to be nonsyndromal. Prevalences of syndromal and nonsyndromal cases were 0.17 and 0.51 per 10,000 live births and fetal deaths, respectively.

Infant and parental characteristics of cases and controls with relative risks and 95% confidence intervals are presented in Table I. Among cytogenetically abnormal cases, females had a nearly 2.5 times greater risk

TABLE I. Relative Risks (Odds) and 95% Confidence Intervals for Holoprosencephaly Cases, California 1983–1988

	Cytogenetically abnormal (n = 50)		Cytogenetically normal[c] (n = 53)		Controls (n = 5,000)
	n[a]	OR (95% CI)[b]	n	OR (95% CI)	n
Child's sex					
Male	16	1.0 —	25	1.0 —	2,605
Female	34	2.3 (1.2, 4.4)	28	1.2 (0.71, 2.1)	2,395
Maternal race/ethnicity					
White, non-Hispanic	24	1.0 —	21	1.0 —	2,736
White, Hispanic	10	0.93 (0.41, 2.0)	17	1.8 (0.90, 3.6)	1,230
Black, non-Hispanic	4	1.3 (0.36, 3.8)	4	1.4 (0.41, 4.4)	366
Asian, non-Hispanic	5	1.6 (0.53, 4.4)	2	0.72 (0.12, 3.2)	361
Other, non-Hispanic	3	1.5 (0.35, 5.1)	4	2.2 (0.64, 6.9)	234
Other, Hispanic	0	—	2	10.9 (1.7, 52.1)	24
Paternal race/ethnicity					
White, non-Hispanic	23	1.0 —	18	1.0 —	2,606
White, Hispanic	9	0.84 (0.36, 1.9)	16	1.9 (0.92, 3.9)	1,219
Black, non-Hispanic	4	1.0 (0.30, 3.2)	4	1.3 (0.38, 4.2)	438
Asian, non-Hispanic	8	2.5 (1.0, 5.9)	2	0.8 (0.13, 3.6)	364
Other, non-Hispanic	1	0.53 (0.03, 3.7)	4	2.7 (0.78, 8.7)	212
Other, Hispanic	0	—	1	9.6 (0.45, 76.4)	15
Maternal birthplace					
California	24	1.0 —	24	1.0 —	2,463
U.S. (Excludes CA)	7	0.59 (0.23, 1.5)	11	0.93 (0.43, 2.0)	1,214
Mexico	5	0.90 (0.30, 2.5)	12	2.2 (1.0, 4.5)	571
Elsewhere	9	1.2 (0.53, 2.8)	3	0.41 (0.10, 1.4)	748
Maternal age (years)					
<20	5	0.95 (0.30, 2.8)	8	2.2 (0.81, 5.9)	514
20–24	7	0.51 (0.19, 1.3)	14	1.5 (0.63, 3.5)	1,333
25–29	16	1.0 —	11	1.0 —	1,560
30–34	10	0.85 (0.36, 2.0)	13	1.6 (0.68, 3.9)	1,142
>34	8	1.7 (0.68, 4.3)	5	1.6 (0.48, 4.9)	449
Paternal age (years)					
<20	3	1.8 (0.41, 6.9)	1	0.50 (0.02, 3.6)	182
20–24	6	0.71 (0.24, 2.0)	6	0.58 (0.20, 1.6)	931
25–29	13	1.0 —	16	1.0 —	1,442
30–34	14	1.2 (0.54, 2.7)	12	0.84 (0.37, 1.9)	1,281
>34	7	0.76 (0.27, 2.0)	8	0.70 (0.28, 1.7)	1,025
Plurality					
Singleton	45	1.0 —	50	1.0 —	4,900
Twins or more	0	—	1	0.98 (0.05, 6.7)	100
No. of previous livebirths					
0	16	1.0 —	18	1.0 —	2,086
1	17	1.4 (0.68, 3.0)	11	0.82 (0.36, 1.8)	1,562
2	3	0.50 (0.12, 1.8)	11	1.6 (0.72, 3.6)	784
3+	7	1.6 (0.61, 4.2)	6	1.2 (0.44, 3.3)	559

[a] Numbers may not add up to the column total because records with missing values are not shown.
[b] OR, odds ratio; CI, confidence interval.
[c] Includes nonsyndromic cases only.

than males (Table I). In contrast, among cytogenetically normal nonsyndromal cases, females and males were at similar risk. With respect to maternal and paternal race/ethnicity, Hispanic whites had a greater risk than non-Hispanic whites among cytogenetically normal cases (OR = 1.8 and OR = 1.9 for maternal and paternal race/ethnicity, respectively), although the confidence intervals around the point estimates included unity. The race/ethnicity categories representing "other Hispanics" also showed increased risks for cytogenetically normal cases, although the risk estimates were based on very few cases. Consistent with the increased risk for Hispanics observed among cytogenetically normal cases, infants whose mothers were born in Mexico were at greater risk than infants whose mothers were born in California. Among cytogenetically abnormal cases, a 2.5 times greater risk was observed for infants and fetuses with Asian fathers. Although the risks for cytogenetically normal holoprosencephaly were 1.5–2.2 times higher among infants with a mother younger than 25 than among infants whose mothers were 25–29 years old, the confidence intervals around these estimates included unity. Differences in risk estimates associated with paternal age, plurality, and parity were consistent with sampling variability for both case groups.

The anatomic type of the brain defect for cytogenetically abnormal and cytogenetically normal case groups is shown in Table II. The proportion of cases with alobar holoprosencephaly was the same for both groups (46%). However, the anatomic type of holoprosencephaly could not be determined for 30% of the cytoge-

TABLE II. Anatomic Classification of Holoprosencephaly Cases, California 1983–1988

	Total (n = 121)		Cytogenetically abnormal (n = 50)		Cytogenetically normal			
					Non-syndromal (n = 53)		Syndromal (n = 18)	
	n	%	n	%	n	%	n	%
Anatomic type								
Alobar	56	46.3	23	46.0	24	45.3	9	50.0
Semilobar	24	19.8	6	12.0	14	26.4	4	22.2
Lobar	11	9.1	6	12.0	4	7.6	1	5.6
Unknown	30	24.8	15	30.0	11	20.7	4	22.2
Sex ratio (M:F)								
Alobar	27:29		10:13		12:12		5:4	
Semilobar	5:19		3:3		2:12		0:4	
Lobar	4:7		1:5		2:2		1:0	
Unknown	14:16		2:13		9:2		3:1	

netically abnormal cases and 21% of the cytogenetically normal cases. A female excess was observed among case infants with cytogenetic abnormalities and was present in cases with alobar or lobar holoprosencephaly, but mostly the excess was attributed to the cases with unknown anatomic type. Among cytogenetically normal cases, in contrast, a female excess was observed for cases with semilobar holoprosencephaly, although this finding is uncertain given the male excess among cases with unknown anatomic type.

Approximately 75% of the cytogenetically abnormal cases had a diagnosis of Trisomy 13 (Table III). Except for the de novo case and the translocations, all of the cytogenetic abnormalities represented in this series have been reported previously [Siebert et al., 1990]. Among the 18 cytogenetically normal syndromal cases, 14 had monogenic disorders and the other 4 cases were infants of diabetic mothers (Table IV). Autosomal dominant holoprosencephaly was the most commonly identified monogenic type of holoprosencephaly.

Shown in Table V is the distribution of cytogenetically normal cases according to the anatomic type of the brain defect and the facial phenotype. The most severe defect of incomplete forebrain cleavage, alobar holoprosencephaly, was present among 43% of the cases with a major facial phenotype (cyclopia, ethmocephaly, cebocephaly, and median cleft lip), 53% of the cases with agnathia or less severe facial phenotypes, and 50% of the cases with an unknown facial phenotype. The least severe defect of incomplete forebrain cleavage, lobar holoprosencephaly, only occurred among cases with median cleft lip or less severe facial phenotypes. Generally, excepting ethmocephaly, the frequency of occurrence of each of the major facial types was inversely related to its severity (cyclopia [n = 9], cebocephaly [n = 13], median cleft lip [n = 21]). Ethmocephaly and agnathia were the rarest of the facial phenotypes, with only one case of each. As a group, the major facial phenotypes occurred more frequently in females (n = 26) than in males (n = 18). However, cyclopia was almost evenly distributed between females (n = 5) and males (n = 4).

For both cytogenetically abnormal and cytogenetically normal holoprosencephaly, most cases were born alive (Table VI). However, death within the first week of life occurred among 80% of the cytogenetically abnormal cases compared to 32% of the cytogenetically normal cases (Table VI). Conversely, only 2% of cytogenetically abnormal cases survived beyond age one, whereas 30% of the cytogenetically normal cases were alive at age one. Among cytogenetically normal cases, age at death was correlated with the severity of the facial phenotype (Table VII). Although all case infants with cyclopia or ethmocephaly died within the first week of life, 57% of case infants with less severe facies were alive at one year of age (Table VII).

DISCUSSION

This study represents the largest population-based series to date that describes the epidemiologic and clinical characteristics of holoprosencephaly defined by both phenotypic and genotypic characteristics. Our prevalence estimate of 1.2 per 10,000 live births and fetal deaths combined is higher than the estimate for an Italian population reported by Mastroiacovo et al. [1993] of 0.77 per 10,000 births. For live births only, we observed a prevalence of 0.88 per 10,000 live births. This prevalence is higher than the prevalence of 0.56

TABLE III. Cytogenetic Abnormalities Among Holoprosencephaly Cases, California 1983–1988

Cytogenetic abnormalities	n
Trisomies	
Trisomy 13[a]	38
Trisomy 18	3
Trisomy 21	1
Triploidy	1
46,XX, 6q+ (de novo)	1
Deletions	
del(18p)	1
46,XX,del(13)(13pter→13q32:)	1
46,XY,r(13)(p11q31)[b]	1
ring 21	1
Translocations	
46,XY,t(1;2)(p13;p21)	1
46,XY,−15,+der(15)t(3;15)(q13.2;q26.3)[c]	1

[a] Includes 2 cases with translocation trisomy 13.
[b] 400–450 band resolution.
[c] Paternal karyotype: 46,XY,t(3;15)(q13.2;q26.3).

TABLE IV. Syndromal Holoprosencephaly Cases, California 1983–1988

Syndromal cases	n	Description of syndrome
Monogenic holoprosencephaly		
Autosomal dominant	4	Münke et al. [1994]
Autosomal recessive	2	Cohen et al. [1971]; Cohen and Gorlin [1969]
Autosomal recessive with polydactyly	1	Cohen and Gorlin [1991]; Verloes et al. [1991]
Autosomal recessive unknown syndrome[a]	1	
X-linked with fetal hypokinesia	1	Hockey et al. [1988]
Steinfeld syndrome	3	Steinfeld [1982]
Fitch syndrome	1	Fitch et al. [1978]
Hypothalamic hamartoblastoma syndrome	1	Hall et al. [1980]
Other		
Infant of diabetic mother	4	Barr et al. [1983]

[a] Proband had holoprosencephaly, hypertelorism, cleft palate, and VSD. The sibling had cleft palate and motor retardation. The parents were normal.

per 10,000 live births reported by the Spanish Collaborative Study of Congenital Malformations (ECEMC) [Urioste et al., 1988]. In contrast, our estimate of cytogenetically normal live born cases, 0.48 per 10,000 live births, is lower than the estimate reported by Roach et al. [1975] of 0.63 per 10,000 live births in Marion County, Indiana.

It is likely that the observed prevalence of 1.2 per 10,000 births is an underestimate of the incidence (the frequency of this malformation among all conceptions). Our estimate is based on live births and fetal deaths of 20 or more weeks' gestation who had a diagnosis consistent with holoprosencephaly recorded in an inpatient hospital chart or at a genetic center. Cases with mild facial changes who died without any brain imaging or neuropathology studies may have been missed. Further, all cases terminated prior to 20 weeks gestation, and those terminated after 20 weeks gestation as outpatient procedures with no follow-up autopsy were also not included. The prevalence of holoprosencephaly among pregnancies terminated at less than 20 weeks gestation has been reported to be over 30 times higher than that of pregnancies that progress beyond 20 weeks [Matsunaga and Shiota, 1977].

This study shows increased risks among females, children of Hispanic mothers, and children of Asian fathers for certain subtypes of holoprosencephaly. The female excess observed among cytogenetically abnormal cases is consistent with previous studies of children with Trisomy 13 [Hamerton, 1971; Baty et al., 1994]. However, the increased risks noted for specific race/ethnic groups have not been reported previously. The greater risks we observed for cytogenetically normal holoprosencephaly among white Hispanics than among white non-Hispanics could be partly due to population differences in utilization of prenatal screening and subsequent elective termination.

Compared to most major structural malformations, holoprosencephaly is unusual in that such a large proportion of the cases is associated with either a cytogenetic abnormality (41%) or a monogenic syndrome (12%). The proportion of our live born sample that was cytogenetically abnormal (45%) is consistent with previous observations among live births of a 1:1 ratio between chromosomally normal and abnormal holoprosencephaly [Ming et al., 1976; Laurence and Ishmael, 1969]. The proportion of our sample with a monogenic syndrome may be lower than the "true" population proportion because we did not have complete family history information for all cases.

Significant progress has recently been made in attempts to identify single gene disorders that cause holoprosencephaly. Four genes that are important for forebrain development have been localized and named. Mutations of a gene, designated *HPE3,* linked to chromosome area 7q36 are thought to be responsible for many families with autosomal dominant holoprosencephaly [Muenke et al., 1994]. In addition to holopros-

TABLE V. Anatomic Type of Brain Defect and Facial Phenotype for Cytogenetically Normal Holoprosencephaly Cases, California 1983–1988

	Anatomic type of brain defect (n)[a]				
Facial phenotype[a]	Total (n = 71)	Alobar (n = 33)	Semilobar (n = 18)	Lobar (n = 5)	Unknown (n = 15)
Cyclopia	9	5	2	0	2
Ethmocephaly	1	1	0	0	0
Cebocephaly	13	6	4	0	3
Median CL(P)	21	7	7	3	4
Agnathia	1	0	1	0	0
Less severe	16	9	3	1	3
Unknown	10	5	1	1	3

[a] Listed in order of decreasing severity.

TABLE VI. Type of Birth and Age at Death Among Holoprosencephaly Cases, California 1983–1988

Type of birth	Age at death	Cytogenetically abnormal (n = 50) n	%	Cytogenetically normal (n = 71) n	%
Termination[a]		6	12.0	15	21.1
Stillborn[b]		3	6.0	6	8.5
Liveborn		41	82.0	50	70.4
	0–7 days	33		16	
	8–28 days	2		4	
	1–12 months	5		15	
	Alive at one year	1		15	

[a] Elective terminations occurring after 19 completed weeks gestation.
[b] Fetal deaths occurring after 19 completed weeks gestation.

encephaly and its accompanying facial features, this syndrome has markedly variable expressivity; affected individuals may have only mental retardation, hypotelorism, hypo- or anosmia, single central maxillary incisor, or unilateral cleft lip. This was the most common monogenic form of holoprosencephaly in our study population, with four cases. Among our cases classified as cytogenetically abnormal, we found two with deletions and one with a translocation involving the loci of the other 3 holoprosencephaly genes: *HPE1* at 21q22 involved with ring 21, *HPE2* at 2p21 involved in a translocation t(1;2)(p13;p21), and *HPE4* on 18p involved with a deletion [Muenke et al., 1995; Schell et al., 1996; Overhauser et al., 1995]. Several other chromosomal abnormalities have been associated with holoprosencephaly, but specific *HPE* genes have not been assigned to these loci. These abnormalities include deletions of 13q. We found two infants whose holoprosencephaly probably resulted from deletion of this putative chromosome 13 gene, one involving a ring 13 and the other a deletion of 13q. A recent report of a small interstitial deletion of 13q in a fetus with holoprosencephaly has narrowed the "critical region" to 13q32 [Brown et al., 1995]. This region was deleted in each of our two patients. Together with these previous case reports of the deletion 13q syndrome, our findings suggest that a fifth *HPE* gene should be designated to this chromosomal area of 13q32. (See summary in Siebert et al., 1990.) Lastly, we found one case with an unbalanced translocation that resulted in trisomy for 3p. This abnormality has been reported as a cause of holoprosencephaly before [Siebert et al., 1990].

Our large number of cases of holoprosencephaly allowed us to examine some aspects of the correlation between facial anomalies and brain anomalies. In DeMyer et al.'s [1964] original article, "The face predicts the brain," the authors described a correlation between a graded series of facial anomalies and the graded anatomical spectrum of holoprosencephaly. That is, at the severe end of the spectrum of facial anomalies, cyclopia and ethmocephaly, alobar holoprosencephaly was universal; cebocephaly and median cleft lip were usually associated with alobar holoprosencephaly; and less severe facial anomalies, such as hypotelorism with or without cleft lip, were associated with semilobar or lobar holoprosencephaly. Later observations weakened this correlation, with DeMyer [1977] and others reporting that a number of cases of alobar holoprosencephaly had an unremarkable face. Because we ascertained cases of holoprosencephaly rather than cases with holoprosencephalic face, we could not evaluate how well the face predicts the brain. However, among our cytogenetically normal cases, we could examine the correlation between the degree of forebrain cleavage and the facial phenotype (Table V). Descending through the spectrum of the more severe facial phenotypes (cyclopia, ethmocephaly, cebocephaly, median cleft lip), the correlation between the severity of the facial phenotype and the severity of the brain defect generally held. The relative proportion of semilobar and lobar holoprosencephaly increased as the severity of the facial anomaly decreased. This general trend, however, did not persist for those cases with less severe facies; over half had alobar holoprosencephaly. Thus, our data suggest that the degree

TABLE VII. Age at Death According to Facial Phenotype Among Cytogenetically Normal Liveborn Holoprosencephaly Cases,* California 1983–1988

Age at death	Facial phenotype: Cyclopia (n = 5)	Ethmocephaly (n = 1)	Cebocephaly (n = 11)	Median CL (n = 16)	Less severe (n = 13)
0–7 days	5	1	4	1	4
8–28 days	0	0	1	2	1
1–12 months	0	0	5	10	0
Alive at 1 year	0	0	1	3	8

* For four cases, facial type was unknown, of whom one died within the first week of life, and three were alive at one year of age.

of forebrain cleavage cannot be predicted accurately in a child with a less severe facial phenotype, a position strongly supported by Cohen [1989b].

While the general perception among the clinical genetics community is that nearly all infants with holoprosencephaly die within a few months of birth, there are few data to provide accurate guidance to parents about infant mortality. Recently, Barr and Cohen [1992] reported that 20% of a case series of infants (n = 46) with isolated (nonsyndromal, nonchromosomal) alobar holoprosencephaly were alive at 12 months. Our observation of 30% survival to one year among a clinically comparable, but population-based sample of 50 cytogenetically normal cases is quite similar. Our observation that length of survival was inversely correlated with the severity of the facial phenotype was also noted by Barr and Cohen [1992]. This information should be valuable for providing more specific counseling about infant mortality to families who have delivered a cytogenetically normal, live born infant with holoprosencephaly. For live born infants with holoprosencephaly and a cytogenetic abnormality, our data suggest that parents may be told that three-fourths of those infants die within the first week of life, and that survival to 12 months is very unlikely.

In summary, this large population-based study among over one million live births and fetal deaths provides robust prevalence estimates for subgroups of holoprosencephaly and more accurately describes relationships between those subgroups and a variety of clinical and epidemiologic characteristics than previous institution-based studies of holoprosencephaly.

REFERENCES

Agapitos M, Georgiou-Theodoropoulou M, Koutselinis A, Papacharalampus N (1986): Cyclopia and maternal ingestion of salicylates. Pediatr Pathol 6:309–310.

Barr M Jr, Hanson JW, Currey K, Charp S, Toriello H, Schmickel RD, Wilson GN (1983): Holoprosencephaly in infants of diabetic mothers. J Pediatr 102:565–568.

Barr M Jr, Cohen MM Jr (1992): Survival and performance with isolated alobar holoprosencephaly. Proc Greenwood Genet Center 11:93–94.

Baty BJ, Blackburn BL, Carey JC (1994): Natural history of Trisomy 18 and Trisomy 13: I. Growth, physical assessment, medical histories, survival, and recurrence risk. Am J Med Genet 49:175–188.

Benawra R, Mangurten HH, Duffell DR (1980): Cyclopia and other anomalies following maternal ingestion of salicylates. J Pediatr 96:1069–1071.

Bönnemann C, Meinecke P (1991): Holoprosencephaly as a possible embryonic alcohol effect: Another observation [Letter]. Am J Med Genet 37:431–432.

Brown S, Jackey PE, Lien JM, Warburton D (1995): A small deletion in a putative "critical region" in chromosome 13q32 in a fetus with isolated holoprosencephaly. Am J Hum Genet 57:A109.

Byrne PJ, Silver MM, Gilbert JM, Cadera W, Tanswell AK (1987): Cyclopia and congenital cytomegalovirus infection. Am J Med Genet 28:61–65.

Cohen MM Jr, Gorlin RJ (1991): Pseudo-trisomy 13 syndrome. Am J Med Genet 39:332–335.

Cohen MM Jr, Gorlin RJ (1969): Genetic considerations in a sibship of cyclopia and clefts. In Bergsma D, McKusick V, Hall J, Scott C (eds): "The Clinical Delineation of Birth Defects: Part II. Malformation Syndrome." New York: Alan R. Liss, Inc., for the National Foundation—March of Dimes. BD:OAS 5 (2):113–118.

Cohen MM Jr, Jirasek JE, Guzman RT, Gorlin RJ, Peterson MQ (1971): Holoprosencephaly and facial dysmorphism: Nosology, etiology and pathogenesis. In Bergsma D (ed): "Third Conference on the Clinical Delineation of Birth Defects." Baltimore: for the National Foundation—March of Dimes—by Williams and Wilkins (1971). BD:OAS 7 (7):125–135.

Cohen MM Jr (1989a): Perspectives on holoprosencephaly: Part I. Epidemiology, genetics, and syndromology. Teratology 40:211–235.

Cohen MM Jr (1989b): Perspectives on holoprosencephaly: Part III. Spectra, distinctions, continuities, and discontinuities. Am J Med Genet 34:271–288.

Croen LA, Shaw GM, Jensvold NJ, Harris JA (1991): Birth defects monitoring in California: A resource for epidemiological research. Paed Perinatal Epidemiol 5:423–427.

DeMyer W, Zeman W, Palmer CG (1964): The face predicts the brain: diagnostic significance of median facial anomalies for holoprosencephaly (arhinencephaly). Pediatrics 34:256–263.

DeMyer W (1977): Holoprosencephaly (cyclopia-arhinencephaly). In Vinken PJ, Bruyn GW (eds): "Handbook of Clinical Neurology." Amsterdam: North-Holland Publishing Co., pp 431–478.

EGRET (1991): Statistics and Epidemiology Research Corporation. Seattle, Washington.

Fitch N, Srolovitz H, Robitaille Y, Guttman F (1978): Absent left hemidiaphragm, arhinencephaly, and cardiac malformations. J Med Genet 15:399–401.

Hall JG, Pallister PD, Clarren SK, Beckwith JB, Wiglesworth FW, Fraser FC, Cho S, Benke PJ, Reed SD (1980): Congenital hypothalamic hamartoblastoma, hypopituitarism, imperforate anus, and postaxial polydactyly: A new syndrome? I. Clinical, causal, and pathogenetic considerations. Am J Med Genet 7:47–74.

Hamerton JL (1971): Clinical cytogenetics. In: "Human Cytogenetics, Vol II." New York: Academic Press, pp 1–545.

Hockey A, Crowhurst J, Cullity G (1988): Microcephaly, holoprosencephaly, hypokinesia—second report of a new syndrome. Pren Diagn 8:683–686.

Holmes LB, Harvey EA (1994): Holoprosencephaly and the teratogenicity of anticonvulsants. Teratology 49:82.

Jellinger K, Gross H, Kaltenbäck E, Grisold W (1981): Holoprosencephaly and agenesis of the corpus callosum: frequency of associated malformations. Acta Neuropathol 55:1–10.

Khudr G, Olding L (1973): Cyclopia. Am J Dis Child 125:120–122.

Lammer EJ, Chen DT, Hoar RM, Agnish ND, Benke PJ, Braun JT, Curry CJ, Fernhoff PM, Grix AW, Lott IT, Richard JM, Sun SC (1985): Retinoic acid embryopathy. N Engl J Med 313:837–841.

Laurence KM, Ishmael J (1969): Arhinencephaly and 13-15(D) trisomy. Oxford Chromosome Conf. Proc. Chromosomes Today 2:86–89.

Lison MP, Armbrust-Figueiredo J, Mega D (1967): Arhinencephalia: Considerations à propos a case diagnosed during life. Acta Neurol Belg 67:25–36.

Mastroiacovo P, Botto LD, Cavalcanti DP, Zampino G, Serafini MA (1993): Epidemiological and genetic study of holoprosencephaly in 106 cases observed in the Italian Multicentric Registry 1978–1989. Proceedings of the First International Meeting of the Genetic and Reproductive Epidemiology Research Society (GRERS) 1:71–82.

Matsunaga EI, Shiota K (1977): Holoprosencephaly in human embryos: Epidemiologic studies of 150 cases. Teratology 16:261–272.

Ming P-M, Goodner DM, Park TS (1976): Cytogenetic variants in holoprosencephaly. Am J Dis Child 130:864–867.

Muenke M (1989): Clinical, cytogenetic, and molecular approaches to the genetic heterogeneity of holoprosencephaly. Am J Med Genet 34:237–245.

Muenke M, Gurrieri F, Bay C, Yi DH, Collins AL, Johnson VP, Hennekam RCM, Schaefer GB, Weik L, Lubinsky MS, Daack-Hirsch S, Moore CA, Dobyns WB, Murray JC, Price RA (1994): Linkage of a human brain malformation, familial holoprosencephaly, to chromosome 7 and evidence for genetic heterogeneity. Proceedings National Academy Sciences 91:8102–8106.

Muenke M, Bone LJ, Mitchell HF, Hart I, Walton K, Hall-Johnson K, Ippel EF, Dietz-Band J, Kvaløy K, Fan C-M, Tessier-Lavigne M, Patterson D (1995): Physical mapping of the holoprosencephaly critical region in 21q22.3, exclusion of *SIM2* to a region of chromosome 21 important for Down Syndrome. Am J Hum Genet 57:1074–1079.

Overhauser J, Mitchell HF, Zackai EH, Tick DB, Rojas K, Muenke M (1995): Physical mapping of the holoprosencephaly critical region in 18p11.3. Am J Hum Genet 57:1080–1085.

Probst FP (1979): "The Prosencephalies: Morphology, Neuroradiological Appearances and Differential Diagnosis." Berling: Springer-Verlag, pp 1–25.

Roach E, DeMyer W, Conneally PM, Palmer C, Merritt AD (1975): Holoprosencephaly: birth data, genetic and demographic analyses of 30 families. In Bergsma D (ed): "Papers presented at the Johns Hopkins Hospital." New York: American Elsevier, for the National Foundation—March of Dimes—(1975). BD:OAS (11): 294–313.

Ronen GM, Andrews WL (1991): Holoprosencephaly as a possible embryonic alcohol effect. Am J Med Genet 40:151–154.

Ronen GM (1992): Holoprosencephaly and maternal low-calorie weight-reducing diet. Am J Med Genet 42:139.

Ronen GM, Andrews WL (1991): Holoprosencephaly as a possible embryonic alcohol effect. Am J Med Genet 40:151–154.

Schell U, Wienberg J, Köhler A, Bray-Ward P, Ward DE, Wilson WG, Allen WP, Lebel RR, Sawyer JR, Jacobs PA, Aughton DJ, Punnett HH, Lammer EJ, Kao F-T, Ward DC, Muenke M (1996): Molecular characterization of breakpoints in patients with holoprosencephaly and definition of the *HPE2* critical region in 2p21. Hum Mol Genet 5:223-229.

Siebert JR, Cohen MM, Sulik KK, Shaw C-M, Lemire RJ (1990): "Holoproscencephaly: An Overview and Atlas of Cases." New York: Wiley-Liss, pp 1–397.

Stabile M, Bianco A, Iannuzzi S, Buonocore MC, Ventruto V (1985): A case of suspected teratogenic holoprosencephaly. J Med Genet 22:147–149.

Steinfeld HJ (1982): Case report 81: Holoprosencephaly and visceral defects with familial limb abnormalities. Syndrome Identification 8:1–2.

Urioste M, Valcarcel E, Gomez MA, Pinel I, Garcia de León R, Diaz de Bustamante A, Tebar R, Martinez-Frias ML (1988): Holoprosencephaly and Trisomy 21 in a child born to a nondiabetic mother. Am J Med Genet 30:925–928.

Verloes A, Aymé S, Gambarelli D, Gonzales M, Le Merrer M, Mulliez N, Philip N, Roume J (1991): Holoprosencephaly-polydactyly ("pseudotrisomy 13") syndrome: A syndrome with features of hydrolethalus and Smith-Lemli-Opitz syndromes. A collaborative multicentre study. J Med Genet 28:297–303.

Webster WS, Lipson AH, and Sulik KK (1988): Interference with gastrulation during the third week of pregnancy as a cause of some facial abnormalities and CNS defects. Am J Med Genet 31:505–512.

Yakovlev PI (1959): Pathoarchitectonic studies and cerebral malformations III. Arhinencephalies (holotelencephalie). J Neuropathol Exp Neurol 18:22–55.